UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/063,978	04/21/98	OBREMSKI R	45D-1750(641

HM12/0224

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EXAMINER	
HINES,J	

ART UNIT	PAPER NUMBER
1641	8

DATE MAILED: 02/24/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/063,978	Obremski et al.
Examiner	**Group Art Unit**
Ja-Na Hines	1641

☒ Responsive to communication(s) filed on Dec 13, 1999

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1-26 is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-26 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Amendment Entry

1. Examiner acknowledges amendments to the specification.

Drawings

2. Applicant is required to submit a proposed drawing correction in reply to this Office action. However, formal correction of the noted defect can be deferred until the application is allowed by the examiner.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-4, 13-19, 21 and 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ekins et al., (EP 304,202) in view of Ekins et al., (J. of Clinical Immuno.) Ekins et al., (EP 304,202) teaches the determination of ambient concentrations in liquids for the determination of several analytes, including hormones, proteins, and other naturally occurring of artificially present substances on biological liquids such as body fluids (page 2 lines 5-8). The method of teaches analyzing and measuring "...the concentration of analyte in a fluid sample by

contacting the fluid with a trace amount of a binding agent such as an antibody specific for the analyte in the sense that it reversibly binds the analyte but not other components of the fluid, determining a quantity representative of the proportional occupancy of binding sites n the binding agent and estimating from that quantity the analyte concentration.... ..The amount of binding agent is sufficiently independent of the absolute volume of the fluid and of the absolute amount of binding agent ....and the concentration of the analyte in the fluid is related to the fraction of binding sites on the binding agent occupied by the analyte by the equation" (page 2 lines 11-30). Sample sizes at each location in an individual array may range from 10^5 to 10^{10} molecules of binding agent (page 3 lines 37-40). Understanding that the recognition of such small amounts of binding agents is permissible, next it is feasible to place the binding agent required for a single concentration measurement on a very small area of a solid support and hence to place in juxtaposition to one another but at spatially separate points on a single solid support a wide variety of different binding agents specific for different analytes which are or may be present simultaneously in a liquid to be analyzed (page 4 lines 8-13). Simultaneous exposure of each of the separate points to the liquid to be analyzed will cause each binding agent spot to take up the analyte for which it is specific to an extent representative of the analyte concentration in the liquid (page 4 lines 13-15). These measurements may be performed consecutively, such as using a laser which scans across the support or simultaneously i.e. using a photographic plate depending on the nature of the labels (page 4 lines 21-23). The method for determining concentrations of a plurality of agents comprises: loading a plurality of different binding agents;

contacting the loaded support means with the liquid sample; and measuring a parameter representative of the fractional occupancy by the analytes (page 4 lines 28-44). The support is preferably non-porous so that the binding agent is disposed on its surface and may be made of plastic material such as polystyrene, polyolefins or acrylic or vinyl polymers or glass (page 5 lines 1-11). The support may be coated on micro spheres with uniform layers of binding agents and retained in specific locations or in the form of a sheet or plate which is spotted with an array of dots of binding agents (page 5 lines 12-15). However, this is advantageous because the configuration of the support means to be such that liquid samples of approximate volumes are readily in contact with the plurality of spaced apart locations marked with the different binding agents (page 5 lines 15-18). The binding agents will preferably be monoclonal antibodies which are made by well known methods (page 5 lines 39-41). It is desirable to use labeled binding agents so that the system binding agent/analyte/site-recognition reagent includes two different labels of the same type such as fluorescent or enzymatic (page 5 lines 45-47). The measurement of fluorescent markers of the relative intensity of the signals may be carried out by using a laser scanning confocal microscope or a laser bean which scans the dots on the support to cause fluorescence of the markers and wavelength to distinguish and measure the amount of fluorescence emitted (page 5-6 lines 56-2). In Example 1, the spots on the support are approximately $1mm^2$ and a sample volume of about 400ml or 2.4×10^{10} molecules of analyte. The kit comprises a plurality of standard samples containing known concentrations and a set of

labeled site-recognition reagents (page 4 lines 52-55). However Ekins et al., (EP 304,202) does not teach the analyte being substantially depleted from the sample.

Ekins et al., (J. of Clinical Immuno.) teaches multianalyte immunoassays. Ambient analyte immunoassays essentially rely on the measurement of antibody occupancy (page 172 para.2). This measure the analyte concentration in the medium to which the antibody is exposed (page 172 para. 2). Figure 4 reveals that when an amount of antibody is exposed to an analyte containing medium the resulting occupancy of antibody binding sites solely reflects the ambient analyte concentration (page 173 para. 1). Analyte binding by antibody clearly causes analyte depletion in the surrounding medium (page 173 para. 1)

Therefore, at the time of applicants invention it would have been obvious to use the technique of allowing for analyte depletion in a sample as taught by Ekins et al., (J. of Clinical Immun.) in the binding assay of Ekins et al., (EP 304,202) because this technique is already well known in the art for determining analyte concentration.

4. Claims 1-4, 13-19, 21 and 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ekins et al., (EP 304,202) in view of Ekins et al., (Analytica Chimica Acta.). Ekins et al., (EP 304,202) has been discussed above, however it does not teach the analyte being substantially depleted from the sample. Ekins et al., (Analytica Chimica Acta.) Teaches the development of microspot multi-analyte ratiometric immunoassays using dual fluorescent labeled antibodies. The general principles underlying multi-analyte microspot immunoassays

methodology is discussed , including methodology which teaches measuring of different substances in a defined sample volume (abstract). This measure the analyte concentration in the medium to which the antibody is exposed (page 79 para. 2). Figure 4 reveals that when an amount of antibody is exposed to an analyte containing medium the resulting occupancy of antibody binding sites solely reflects the ambient analyte concentration (page 79 para. 2). Analyte binding by antibody clearly causes analyte depletion in the surrounding medium (page 80 para. 1).

No more than routine skill is required to implement well known techniques such as analyte depletion into the binding assay of Ekins et al. (EP 304,202). Therefore, at the time of applicants invention it would have been obvious to use the technique of allowing for analyte depletion in a sample as taught by Ekins et al., (Analytica Chimica Acta.) in the binding assay of Ekins et al., (EP 304,202) because this technique is already well known in the art for determining analyte concentration.

5. Claims 5-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ekins et al., (EP 304,202) and either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.), in further view of Ullman et al., (US Patent 5,512,659). Ekins et al.(EP 304,202), Ekins et al., (J. of Clinical Immuno.) and Ekins et al., (Analytica Chimica Acta.) have been discussed previously however, none of the Ekins et al., references teach the use of first binding partners, ligands and analyte binding partners. Ullman et al., teaches compositions useful in heterogenous

immunoassays wherein the solid support provides the surface for binding in a liquid medium where the support has specific binding pair members, usually receptors affixed to its surface which are capable of binding a complementary specific binding pair member usually a small molecule, which is bound to a reagent capable of binding the analyte and conjugated to a label (col. 2 lines 12-19). The presence or amount of label is related to the presence or amount of analyte in the sample (col. 2 lines 29-30). These methods are more versatile and convenient that the known methods. Members of a specific binding pair means one of two different molecules, having an area on the surface or in a cavity which specifically binds to and is thereby defined as complementary with a particular spatial and polar organization of the other molecule (col. 6 lines 55-57). The members of the specific binding pairs are referred to as ligand and receptor (col. 6 lines 57-59). These will usually be members if an immunological pair such as antigen-antibody, although other specific binding pairs such as antigen-antibody, although other specific pairs are known, including biotin-avidin (col. 6 lines 59-61). The detection of an analyte can allow binding before or after binding to the support, a conjugate of a receptor to the other molecules and a label is combined with the complex (col. 9 lines 36-38). One method teaches a label bound to a receptor for a small molecule, a first antibody complementary to a first determinant site on an analyte and to which is bound a second antibody complementary to a second determinant on the analyte to which a second small molecule such as biotin and a support to which is bound a receptor such as avidin (col. 9-10 lines 60-2). The antibodies used can be monoclonal or polyclonal (col. 10 lines 3-4). Conjugates are a specific binding pair member such as a ligand or

receptor usually an antibody bound covalently or non-covalently, usually covalently to one or many small molecules or labels (col. 7 lines 55-60). The label can be fluorescers (col. 7 line 66), fluorophores such as derivatives of fluorescein and cyanines (col. 12 lines 38-41). Ullman et al., teaches that it is well known to use antigens covalently linked to an enzyme, a biotinylated antibody, and an avidin coated surface (col. 1 lines 24-26), and biotinylated antibody which is complementary to the analyte used, where receptors other than avidin, including strepavidin, may be attached (col. 15 lines 50-54).

Therefore, it would have been obvious at the time of applicants invention to have used the first binding partner, conjugate, biotin-avidin labels and biotinylated antibodies in the method of Ekins et al., (EP 304,202) in view of either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.) because Ullman et al., teaches that these methods are more versatile and convenient that the known methods.

6. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ekins et al., (EP 304,202), in view of either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.) in further view of Waggoner et al., US Patent (5,368,486). The Ekins et al., references have been discussed previously however, none of the three Ekins et al., references teach the use of cyanine dyes. Waggoner et al., (US Patent 5,268,486) teaches the use of fluorescent cyanine and related polymethine dyes which can be used for detecting the presence of certain proteins (col. 2 lines 1-10). When using the cyanine dyes, a stronger fluorescent or

phosphorescent light intensity signal will be given off because a larger number of dye molecules can be attached to the protein which is being probed (col. 2 lines 18-21). These luminescent polymethine cyanine and related polymethine dyes can label nucleic acids, DNA, drugs, toxins, blood cells, microbial materials, particles, plastic, or glass surfaces (col. 2 lines 58-63). The dyes are advantageously soluble in aqueous or other mediums in which the labeled material is contained (col. 2 lines 64-66). "The biological preparation is then subjected to a variety of excitation wavelength, each excitation wavelength used being the excitation wavelength of a particular conjugated dye. A luminescence microscope or other luminescence detection systems, having filters or monochrometers to select the wavelengths of luminescence is employed to determine the intensity of rays of emission wavelength corresponding to the excitation wavelength. The intensity of luminescence at wavelengths corresponding to the emission wavelength of a particular conjugated dye indicates the quantity of antigen which has been bound to the antibody to which the dye is attached" (col. 4 lines 2-17). The dyes have a particular excitation wavelength that correspond to a particular excitation light source such as a laser (col. 4 lines 45-49). When the labels are conjugated to a labeled component they can be excited by light in wavelength regions ranging from 450-900nm (col. 5 lines 55-59). Arylsulfonate or arylsulfonic acid substituted dyes which are types of cyanine and polymethine dyes are intrinsically more fluorescent and have improved photostability and water solubility as compared to dyes without arylsulfonate or arylsulfonic acid group (col. 6 lines 53-57).

Therefore, it would have been obvious at the time of applicants invention to have used cyanine dyes as taught by Waggoner et al., in the method of Ekins et al., (EP 304,202) in view of either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.) because Waggoner et al., teaches that these cyanine dyes are intrinsically more fluorescent; have improved photostability; improved water solubility; can label a wide variety of biological materials; and subject to a variety of excitation wavelengths using lasers.

7. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ekins et al., (EP 304,202) in view of either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.) in view of Waggoner et al., US Patent (5,368,486) in further view of Lee et al., (US Patent 5,453,505). Ekins et al., (EP 304,202), Ekins et al., (J. of Clinical Immuno.), Ekins et al., (Analytica Chimica Acta.) and Waggoner et al., have been discussed previously however, none teaches the use of Cy5 or Cy7. Lee et al., teaches cyanine dyes substituted with either an N-heteroaromatic ion or an iminium ion which have a fluorescence absorbance of between 500 and 900 nm, a reduced tendency to aggregate and enhanced stability (col. 2 lines 23-29). The photostability of several cyanine dyes, including Cy5 and Cy7, which are penta- and hepta-methine derivatives, respectively, are from a class of arylsulfinate dyes was described (col. 18 lines 55-58). The most stable dye was found to be the dye with the shortest wavelength, Cy5 whose structure contains five methine groups, while the remaining dyes contain seven methine groups, such as Cy7 which has similar stability (col. 19 lines 5-8).

Therefore, it would have been obvious at the time of applicants invention to have used Cy5 or Cy7 as taught by Lee et al., in the method of Ekins et al., (EP 304,202) in view of either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.), and Waggoner et al., US Patent (5,368,486), because Lee et al., teaches a reduced tendency to aggregate and enhanced photostability.

8. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ekins et al., (EP 304,202) in view of either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.) in view of Northrup et al (US Patent 5,639,423). Ekins et al., (EP 304,202) in view of either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.) have been discussed previously however, none of the Ekins et al., references teach the use a printer jet to form the array. Northrup et al., teaches an instrument for use in in situ chemical reactions in a microfrabricated environment , which is especially advantageous for biochemical reactions (col. 3 lines 38-41). Reagents may be immobilized onto a micro instrument using a modified jet printer (col. 4 lines 37-40).

Therefore, it would have been obvious at the time of applicants invention to use the well known method of dispensing material using a jet printer as taught by Northup et al., in the method of Ekins et al., (EP 304,202) in view of either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.) because Northup et al., teaches that the method is especially advantageous for biochemical reactions.

Response to Arguments

9. Applicant's arguments with respect to claims 1-26 have been considered but are moot in view of the new ground(s) of rejection.

10. Claims 1-4, 13-19, 21 and 23-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Ekins et al., (EP 304,202) is withdrawn in view of applicants arguments.

11. Claims 5-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ekins et al., (EP 304,202), in view of Ullman et al., (US Patent 5,512,659) is withdrawn in view of applicants arguments.

12. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ekins et al., (EP 304,202), in view of Waggoner et al., US Patent (5,368,486) is withdrawn in view of applicants arguments.

13. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ekins et al., (EP 304,202), in view of Waggoner et al., US Patent (5,368,486) in further view of Lee et al., (US Patent 5,453,505) is withdrawn in view of applicants arguments.

14. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ekins et al., (EP 304,202), in view of Northrup et al (US Patent 5,639,423) is withdrawn in view of applicants arguments.

Prior Art

15. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Ekins et al., (Ann.Biol. Clin.), teaches multispot, multianalyte and immunoassays.

Ekins et al., (J of Biolum and Chemilum), teaches high specific activity of fluorescent markers. Ekins et al., (US Patent 5,526,635) teaches binding assays employing labeled reagents. Ekins et al., (US Patent 4,745,072) teaches immunoassays and immunometric assays of free ligand concentrations in biological fluids. Ekins et al., (EP 134,215) teaches measuring analyte concentration. Ekins et al., (EP 271,974) teaches determination of analyte concentration using two labeling markers.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is (703) 305-0487. The examiner can normally be reached on Monday through Thursday from 6:30am to 4:00pm. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Ja-Na Hines

February 15, 2000

James C. Housel 2/24/00

JAMES C. HOUSEL
SUPERVISORY PATENT EXAMINER